Genetics, lifestyle and longevity: Lessons from centenarians

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Review

Genetics, lifestyle and longevity: Lessons from centenarians

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ABSTRACT

Longevity as a complex life-history trait shares an ontogenetic relationship with other quantitative traits and varies among individuals, families and populations. Heritability estimates of longevity suggest that about a third of the phenotypic variation associated with the trait is attributable to genetic factors, and the rest is influenced by epigenetic and environmental factors. Individuals react differently to the environments that they are a part of, as well as to the environments they construct for their survival and reproduction; the latter phenomenon is known as niche construction. Lifestyle influences longevity at all the stages of development and levels of human diversity. Hence, lifestyle may be viewed as a component of niche construction. Here, we: a) interpret longevity using a combination of genotype-epigenetic-phenotype (GEP) map approach and niche-construction theory, and b) discuss the plausible influence of genetic and epigenetic factors in the distribution and maintenance of longevity among individuals with normal life span on the one hand, and centenarians on the other. Although similar genetic and environmental factors appear to be common to both of these groups, exceptional longevity may be influenced by polymorphisms in specific genes, coupled with superior genomic stability and homeostatic mechanisms, maintained by negative frequency-dependent selection. We suggest that a comparative analysis of longevity between individuals with normal life span and centenarians, along with insights from population ecology and evolutionary biology, would not only advance our knowledge of biological mechanisms underlying human longevity, but also provide deeper insights into extending healthy life span.

Contents

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Age, I do abhor thee, youth, I do adore thee — Shakespeare (1599).

Man …possesses the power of modifying, at least to appearance, the laws of nature affecting him, and perhaps causing a progressive movement, tends to approach a happier physical condition — Quetelet (1842).

From them (centenarians) we can learn how to create our own Blue Zones and start on the path to living longer, better lives — Buettner (2012).

1. Introduction

An incessant desire to attain immortality or at the very least greater longevity, and strategies to achieve it, have been recurring themes among the world's mythologies (Witzel, 2013), and continue into our own times (Stambler, 2014). Fundamental insights into birth, growth and death (demographic) processes in human populations are gleaned from the Gompertz-Makeham (Finch, 2007), and Malthusian population laws (Malthus, 1798). Later, Quetelet (1842) systematically investigated the plausible biological and other causes of demographic processes. He questioned, "What are laws of human reproduction, growth and physical force … the laws of mortality … what influence has nature over man, what is the measure of its influence, and of its disturbing forces; what have been their effects for such a period…" and concluded that, "Of all the causes which modify the mortality of man, none exercises a greater influence than age." Research on the evolutionary genetic bases of biological diversity for over a century has shown that longevity, like any other quantitative traits, varies among individuals, and it is influenced by the interaction of both genetic (nature) and numerous environmental factors (nurture; sensu, Galton, 1890). Availability of food resources, improved living conditions and advances in basic and medical sciences have greatly extended the life span globally (Vaupel, 2010), since Quetelet's fundamental work on factors influencing the life span of an "average man." In some countries, the modal age of death or the age at which highest mortality occurs in any given population, has steadily increased even in the last fifty years (Horiuchi et al., 2013). Detectable evolutionary changes in modern humans could occur even in such a short span of time (Byars et al., 2010; Milot and Pelletier, 2013), and these changes could have a direct impact on longevity. Despite advances in demography and genetics (Charlesworth, 1980; Wachter et al., 2013), "Aging remains one of life's great unsolved riddles" (Anton, 2013). In view of burgeoning challenges posed by the ever-increasing elderly population, it is critical to understand the components of nature and nurture and the relative magnitude of their contribution to healthy aging.

Comparative analyses of life span across wide-ranging taxa have suggested that longevity has an evolutionary basis (Carey, 2003; Wachter et al., 2013). Individuals not only differ in their sensitivity to environmental variations, but also show differential survival and reproduction, in response to such variations, also called natural selection. Environment affects every aspect of viability of individuals from the time of conception to death — they are surrounded by it, respond to it, exploit it and also actively construct it (Lewontin, 2000). The latter process has been termed niche construction, which is broadly defined as "the process whereby organisms, through their metabolism, their activities and their choices, modify their own and/or each other's niches" (Odling-Smee et al., 2003).

An individual or groups of individuals modify their own environment as well as that of others in infinite ways. Some of these modifications, including the ones related to life style could have either proximate or lasting (ultimate – evolutionary) effects on health and longevity of specific individuals, families or larger groups. Many aspects of environmental variation and lifestyle changes (LSC) on longevity are inextricably linked, and often difficult to uncouple. Despite their apparent equivalence, LSC represents a "volitional behavior on the part of an individual" (Egger and Dixon, 2014) and their conscious efforts and choices: education, housing, physical activities, food, drinking and smoking habits, clothing, medical intervention, cultural and religious beliefs, social networks, and so forth. Hence, it is reasonable to suggest that the individual components of the environment and LSC could have either additive or multiplicative or both effects on health and longevity. In an ecological sense, the terms environment and life-style could be equated to niche (Hutchinson, 1957) and niche construction concepts (Lewontin, 2000; Odling-Smee et al., 2013), respectively. From a genetic perspective, gene specific polymorphisms are known to exert differential influence on longevity and its correlated traits. While ecological/environmental factors might have a common influence on all individuals of a group/community, specific aspects of niche construction activities or LSC could exacerbate individual differences. Together these factors would exert synergistic or antagonistic, as well as temporally and spatially heterogeneous effects on longevity at all levels of biological hierarchy: cell, tissues, and individuals within and across generations. These effects could lead to differential viability and reproduction of individuals, which ultimately affect the evolutionary trajectories of individual populations (Odling-Smee et al., 2013; Laland et al., 2014). Here we briefly review the interrelationships among genetic, epigenetic, environment and life style factors influencing life span — normal or exceptional.

We have the following objectives: a) to describe the diversity of longevity phenotype among human populations, b) to identify links among genotypic, epigenetic and phenotypic aspects of longevity from the G–P map perspective, and c) to discuss modulation of healthy longevity (health span) through lifestyle changes in the context of niche construction, and reaction norm concepts. We conclude that while there are opportunities for augmenting healthy life span, there are biological constraints as well. We extend the genotype–phenotype (G–P) map metaphor (Lewontin, 1974; Houle et al., 2010) for this purpose, and briefly describe the role of each of the three (genotype-epigenetic-phenotype; G-E-P) spaces as well as discuss their cumulative influence on longevity. We define life span, life expectancy and longevity as species, population and individual specific processes, respectively. Briefly, life span refers to average life expectancy for an individual between birth and death, and hence has a predictive aspect to it. Longevity, on the other hand, is a more elusive concept and is defined as an individual's ability to reach longer life span under ideal or prevailing conditions (Carey, 2003). We use life span and longevity interchangeably.

2. Diversity of life span in modern humans

It is often suggested that the origins of agriculture, coupled with the establishment of settlements ~10,000 years BP (Skoglund et al., 2012) have brought forth many biological changes in human populations (Larsen, 1995), including human longevity. Examples include: increased availability of protein and calories, habitation, cooking and formation of social structure (Finch, 2007; Finch and Singer, 2014). For instance, Fumagalli et al. (2011) reported a close concordance between variation of a large number of SNPs and environmental variables such as climate, diet regime and pathogen loads. Of these, demographic and pathogen pressure have been found to have stronger influence on human variation across populations. However, human life span, an aspect of demography, might have stayed around 40 years for a long time and may still be at similar levels in some hunter–gatherer groups. This trend appears to have increased since 1600 AD, in most human societies in four phases: urbanization, improved sanitation and nutrition, immunization and modern medicines (Fig. 1; Finch, 2007). Interestingly, Quetelet reported that the average life span was only 32.15, 32.2 and

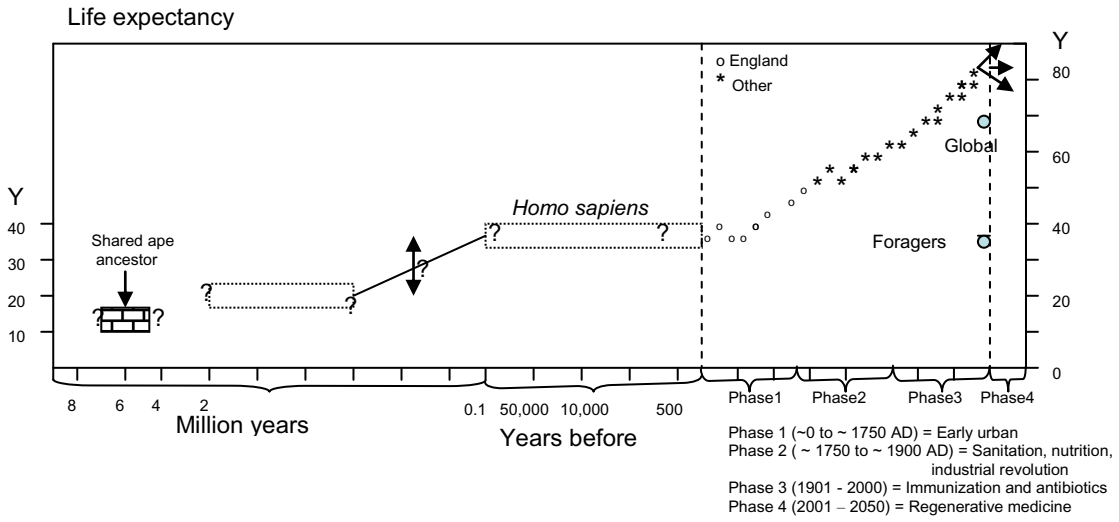

Fig. 1. Human life expectancy through the ages. Note the average life expectancy among foragers has not changed much. Figure modified from Finch (2007) with permission.

33 years, respectively in Belgium, France and England (Quetelet, 1842); yet he also recorded the presence of 16 centenarians on January 1831 in Belgium, the oldest among them being 111 years.

Life expectancy among contemporary human populations ranges from 47.5, 78.8 and 87.2 years in Sierra Leone, United States and Monaco, respectively, with a median of 71.3 (Anonymous, 2012). Centenarians, on the other hand, live for 100–110 years and supercentenarians for 111–122.3 years (Carey, 2003). Thus, centenarians form a distinct group and provide an upper range as well as a bound for human life span. Assuming that Quetelet's estimation was based on accurate records, one could argue that the uppermost bounds of phenotypic diversity of human longevity have not changed dramatically in the last two centuries, despite their gradual numerical abundance among global populations in the last few decades (Meyer, 2010).

3. Aspects of genotype-epigenetic-phenotype (G–P map) relationships

3.1. Molecular genetic aspects (genotype space)

By definition, quantitative traits are influenced by many genes (polygenic) that are located in the nuclear and the mitochondrial genome, as well as interactions among them. The following approaches have been employed to chart the genomic architecture of longevity: candidate gene analysis, linkage and linkage disequilibrium mapping, copy number variation and more recently, exome and whole genome sequencing. These approaches have revealed that 100s of genes and genomic regions may be influencing longevity, lending support to the conclusions drawn by earlier theoreticians, particularly Kimura and Crow (1964), who suggested that genetic variation among quantitative traits may be explained using the infinite allele model (Houle et al., 2010). For instance, Budovsky et al. (2013) have listed between 300 to over 750 genes that are known to influence longevity in humans. This list does not, however, include copy number variation and rare alleles. Dato et al. (2013) and Shadyab and LaCroix (2014) listed many genes including mitochondrial ones, that have been consistently shown to influence human longevity: APOE1, ATM, BCL, CETP, eNOS, FOXO1A, FOXO3A, KLOTHO, LMNA, TERC, HSPA, SOD1, 2, 3, NIOS1, 2, 3, P53, RAGE and others. Some of these genes are known to play an important role in cellular and metabolic functions such as development (FOXO1), oxidative stress (SOD3; HSPA), genome maintenance (P53), cognitive pathways (ApoE), lipid metabolism (APOE, CETP), and glucose metabolism (IGF1). For instance, in a comprehensive study, Beekman et al. (2013) reported that a variant close to APOE gene was found to be associated with 90 year olds in the European Genetics of Healthy Aging study (GEHA). Further analysis suggested that one of the isoforms of APOE2 was associated with longevity. All of these genes show epistatic and pleiotropic effects on various pathways. For instance, IGFR is associated with short stature, which in turn is associated with longevity in humans (van Heemst, 2010; Bartke, 2008, 2012). Similarly, FOXO3A is involved in cellular processes, and it is over represented in long-lived Okinawans (Willcox et al., 2008) and Germans (Flachsbart et al., 2009). Clearly, all or a subset of these genes must exert pleiotropic effect on longevity throughout a life span. Such genes may be treated as genes that exert moderately positive and contextual effects on both longevity and its antecedent component traits (Parsons, 2007; Wachter, 2014).

3.2. Epigenetic aspects (space)

Information from the genotype space passes through developmental space and expresses as phenotype under the influence of environment. Waddington (1942) coined the term "epigenetics" to represent "concatenations of processes linked together in a network," that take place in the space embedded between the genotype and the phenotype. He later described epigenetics as a "branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being" (Waddington, 1975). In short, epigenetic space consists of causal sources, direction of their flow and their effects between the genotype and the phenotype spaces as originally conceived by Wright (1934). Remarkably, more recent studies have confirmed these insights and suggest that epigenetic processes involve direct, indirect, mediated, conditional, reverse, truncated and merged paths of distribution and dissipation of gene specific enzymes as well as post-translational modifications of histones into various components of the phenome (extra-genome) (Hallgrimsson and Hall, 2011). The Wright–Waddington fields of epigenetic networks are common features of all cellular (Karlebach and Shamir, 2008) and metabolic processes and in metabolic disorders (e.g., Seashore and Wappner, 1996). These diverse epigenetic processes initiate as well as orchestrate phenotypic expression in relation to both constant and constructed environments. The role of epigenetic factors on human development and disease has been discussed by Gluckman et al. (2011). An example of these relationships with respect to factors affecting longevity may be seen in Fig. 3.

Aging is invariably a time-dependent deteriorative process. It affects various component systems of the human body at different rates, ranging from physiological, anatomical to morphological traits. This deteriorative process is frequently seen in the functional decline of organs, fertility and viability fitness (Darwinian fitness) as well as

increased levels of disease susceptibilities (Kirkwood and Austad, 2000; Finch, 2007). Then, do epigenetic mechanisms track age and stage related developmental changes? Although there are several epigenetic mechanisms (e.g., imprinting, microRNAs, and SiRNA), much of the contemporary research on epigenetics focuses on measuring changes in chromatin structure (methylation patterns) that influence age-specific cellular epigenetic landscape (Goldberg et al., 2007). Richardson (2003) studied methylation patterns of over 200 loci among three age groups: newborn, middle-aged and the elderly. He reported both distinct patterns of gene expression and hierarchical differentiation: within individuals, among individuals within families as well as among the three age groups. Similarly, Johansson et al. (2013) studied methylation patterns in relation to aging among seven age groups ranging from 14 to 94. They reported that, with age while 60% became hypomethylated, 39.5% showed hypermethylation, and concluded that age appears to affect 29% of the sites. In an interesting study, Heyn et al. (2012) compared methylation patterns between newborns and centenarians, and found divergent methylation patterns as expected. Centenarians showed relatively greater levels of hypomethylation compared to the newborns, and the "DNA obtained from a 103-year-old donor was more unmethylated overall than DNA from the same cell type obtained from a neonate." Intermediate levels of methylation status were observed for the middle age group. Using white blood cells among differing age groups, Weidner and Wagner (2014) also obtained very similar results and reported that while certain markers showed a linear relationship with age others did not. Clearly, the magnitude of epigenetic changes during the aging process suggests that gene action largely tracks phenotypic variation and covariation among traits, via epigenetic mechanisms. It could also vary in direction, strength and context as previously reported by various investigators using quantitative genetic approaches (Hughes and Charlesworth, 1994; Snoke and Promislow, 2003; Furrow et al., 2013; Govindaraju et al., 2014; Milot et al., 2014). In general, these investigators have demonstrated that during the aging process variances, covariances as well as heritability estimates could monotonically increase, decrease and even fuctuate reflecting the underlying epigenetic processes.

3.3. Phenotypic diversity of longevity as a composite trait (phenotype space)

Global variation of human life span among individuals could be broadly divided into two categories: those who reach the maximum average life expectancy (i.e., 87.2 in Monaco and 71.3 global average) in contemporary human populations and those who exceed this bound (i.e., live beyond 100 years) or centenarians. There is a clear disconnect between the group that conforms to "ordinary" life span (as seen in general populations) and the group with "extra-ordinary" life span, with "unusual and differential longevity" (i.e., centenarians; Caselli and Luy, 2013). The latter group differs from the former by at least 3 SD (or by about 25 years) and forms a distinct group in the distribution of life span in contemporary human populations (Fig. 2).

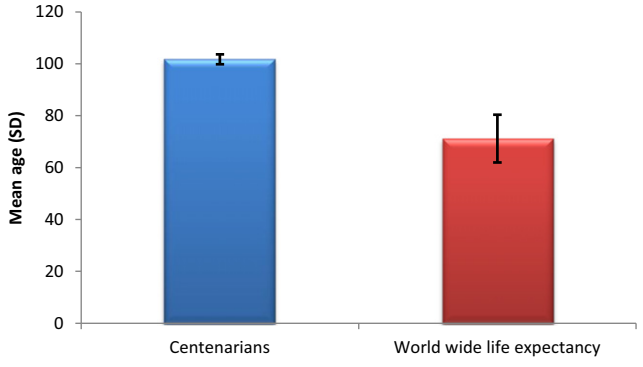

Fig. 2. Comparison between the average life span of centenarians in a British cohort, relative to average life expectancy among contemporary human populations. Mean death age of British centenarians and the average life expectancy of global populations differ by 3.0 SDs (Evans et al, 2014; Annonymous, 2012).

Therefore, exceptional longevity may be viewed as a threshold trait because it is expressed only among a limited number of individuals at the extreme end of the distribution range (Falconer and Mackay, 1996). Because of the out-breeding nature of our species, there is more variation among individuals within populations for any given trait, including longevity, than among populations (Lewontin, 1972; Steele et al., 2014; Mather and Jinks, 1982; Witte et al., 2014). Accordingly, each individual perceives and responds to both common and constructed environments differently — a phenomenon called environmental sensitivity, which itself contributes a fraction of variation to the total genetic variation represented in the heritability estimates (Hill and Mulder, 2010). Variation attributable to ontogeny among specific individual phenotypes may serve as targets of age/stage specific selection (Wright, 1934; Mayr, 1976; Dmitriew et al., 2010).

Heritability is an important population parameter employed to measuring quantitative genetic variation. It is a measure of the portion of genetic information that progeny receive from their parents for a given trait in a population at a specific time. Although there are many reports on the heritability of longevity, perhaps the work on Danish Twin Study by Herskind et al. (1996), still remains as the best representative of most of these studies. While these investigators reported a heritability of 0.23 and 0.26 for males and females, respectively, Mitchell et al. (2001) found 0.25 in the old-order Amish. By extension, we could use 0.30 as a general index of heritability of longevity (Finch and Tanzi, 1997). This suggests that variation stemming from factors attributable to environment and niche construction may exert an overwhelming influence on individual's life span. It is worth noting that variations among individual phenotypes are used as indices to estimate variance and covariances among them, which in turn are used to estimate heritabilities and co-heritabilities. Comstock (1960), however, cautioned that variance estimates, "at best are …elusive quantities," as they are affected by numerous genetic, demographic and environmental factors. It follows that, heritability estimates derived from elusive quantities should remain elusive as well. In general, because of the low and fluctuating nature of heritability estimates for longevity or any other fitness traits, they serve as less reliable indices of evolutionary fitness (Hansen et al., 2011).

Longevity as a composite life history trait, is influenced by other life history traits such as body weight, age to maturity, and number of offspring, (Carey, 2003) and subcomponents of each of these traits; hence, ideally covaries with all or most of these traits during the growth and development (Hughes and Charlesworth, 1994; Snoke and Promislow, 2003) and in relation to environments (Dmitriew et al., 2010). During the aging process, individual specific system-wide changes are initiated at the zygotic stage and progress till death. Such cumulative changes progressively perturb (wear-and-tear) the axial relationships among many biochemical, anatomical and morphological traits over a life course (Govindaraju et al., 2014; Milot et al., 2014), which are generally described as "frailties" (Fulop et al., 2010).

3.4. Environmental factors

Individuals are not only born with a distinct genetic, biochemical and morphological "individuality" (Garrod, 1931; Williams, 1956), but because of this unique feature, they exploit and react differently to both micro- and macro-environmental factors from conception to death. Micro-environment refers to an individual and his/her immediate surroundings, spanning biological (family) and physical entities (household). Macro-environment, on the other hand, refers to much boarder categories such as climate, landscape, and social and cultural conditions, and facilitates adaptations in humans (Hancock et al., 2011). Environmental factors could trigger a series of coordinated changes in the physiological and developmental patterns and produce

alternative phenotypes during the life-course of an individual — a process commonly referred to as developmental plasticity. These changes might also have beneficial health effects. Accordingly, certain regions around the globe, the "Blue Zones": Okinawa, Nicoya, Ikaria, Sardinia, Loma Linda, in Japan, Costa Rica, Greece. Italy and Mexico (Poulain et al., 2013) may be more conducive to fostering longer life span relative to most other regions of the world. It appears that even Quetelet (1842) contemplated on such possibilities, as he suggested that "out of 16 centenarians found in Belgium fourteen of them lived in the three provinces of Hainault, Namur and Luxembourgh … the oldest individuals 104, 110 and 111 years. They belonged to the province of Luxembourg." It is worth noting that the maximum life span (MLS) in the population he studied, was about 111 years, while it is 122.3 years at the present time.

3.4.1. Niche construction

Relative to most organisms, humans actively and consciously "construct" their own extensive and elaborate environments. These include food, clothing, shelter, medical interventions, transportation, and landscapes, to name a few. All of these may exert both advantageous and adverse effects on longevity at all levels of biological organization during the course of their development. These combined processes have been termed "niche construction" (Odling-Smee et al., 2013; Lewontin, 2000), which has been suggested to influence evolutionary processes in a wide-range of organisms, including humans (Laland et al., 2014; Laland, 2014; Bateson, 2013). Four broad aspects of niche construction might have contributed to human longevity in phases, in the last four centuries: early urban, industrial revolution coupled with sanitation and nutrition, immunization and antibiotics and regenerative medicine (Finch, 2007). Interestingly, however, life expectancy among a few hunter–gather communities appears to have remained roughly around 40 years, in the same period (see the dot in Fig. 1). Hence, it is conceivable that a sustained trend of niche construction activities (aspects of nurture) over the last four centuries might have contributed significantly toward increasing life expectancy among global populations.

4. Phenotypic variation and niche construction

Traditionally, phenotypic variation (*Vp*) is partitioned into genetic (*Vg*) and environmental (*Ve*) variance components (Falconer and Mackay, 1996). From the niche construction perspective, however, individual genotypes would ideally interact with two different environments — a regular one and a constructed one. Extending the familiar quantitative genetic model employed to partitioning phenotypic variation (e.g., Falconer and Mackay, 1996), these may be expressed as: $P = G + Er + Enc + G \times Er + G \times Enc$, where, P = phenotype (longevity); G = genotype; Er = regular environment; Enc = environment (created by) niche construction; $G \times Er$ = interaction of a genotype in a regular environment; $G \times Enc$ = genotype response to a constructed environment. The influence of the constructed environment on a given genotype may be represented as, $G = G \times Enc = G^*$ (Goodnight, pers. comm. 2014). It is assumed that *Enc* (just as *Er*) would also influence the additive (*A*), dominant (*D*) and epistatic (*E*) components of the genotype (*G*) and their interactions thereof (Falconer and Mackay, 1996). In other words, novel and unique environments derived from niche construction could potentially affect phenotypic expression of quantitative traits through various components of genotype and epigenetic spaces (Furrow et al., 2013). As a result, both positive and negative influences of niche construction on health and longevity may be expected at all levels of biological hierarchies — cells to populations. Individual genotype specific responses to composites (i.e., regular and constructed) of environmental variations over the life course may be best represented by the concept of norms of reaction (Gupta and Lewontin, 1982; Wells and Stock, 2011). The concept of reaction norm deals with altered phenotypic expression across environments without involving DNA sequence changes. By extension, epigenetic processes essentially represent all biological phenomena underlying reaction norms and these have evolutionary potential (Stearns, 2014).

The four transitions that have contributed to human longevity in the last five centuries, viz., urbanization, improving sanitation and nutrition, immunization and modern medicines (Finch, 2007) may be interpreted in terms of cultural niche construction (Borenstein et al., 2006). By analogy, the essential aspects of these transitions over millennia point toward sustained lifestyle changes and hence, niche construction. Such changes may have both beneficial and harmful effects on evolutionary fitness (Laland et al., 2014; Laland, 2014; Odling-Smee et al., 2013). For instance, Egger and Dixon (2014) listed various components of modern life-style such as improvement in living conditions, food availability, and medicine. These authors have also discussed how life-style changes are contributing to epidemics such as metabolic syndrome, obesity and sequelae of other diseases: endocrine/metabolic, gastrointestinal, kidney, mental/CNS health, musculoskeletal respiratory, reproductive, dermatological and many others. All of these could influence individual specific as well as age and stage dependent morbidity and mortality patterns, which in turn could also affect both viability and reproductive (evolutionary) fitness.

4.1. Life-style changes and metabolism

Excessive or restricted food consumption (calorie restriction, CR) provides an excellent example of both life-style modification and niche construction. While excessive food consumption leads to metabolic syndrome and reduced longevity, calorie restriction has been shown to increase longevity in many organisms, including mammals. Nutritional interventions, coupled with CR and associated approaches that are part of life-style changes, singly or in combination appear to enhance longevity, at least in model organisms (Masoro, 2005; Mair and Dillin, 2008), mediated by epigenetic process such as transcription, metabolism and reducing insulin levels. Based on studies on diverse model organisms, it has been argued that CR could help maintain prolonged health and to some extent even restore it, through plastic responses, as CR affects three critical nutrient sensors, AMPK, SIRT1 and mammalian target of rapamycin (mTOR) (Finch, 2007). Additionally, CR also influences inflammation, cell survival, stress defense, autophagy and protein synthesis (Fig. 3; Barzilai et al., 2012), which are well-known to mediate the aging process (Finch, 2007).

Calorie restriction may not be a panacea for decelerating the aging process, however. Individuals that restrict their calorie intake also show correlated multi-system negative effects — reduced bone density and muscle mass as well as increased lethargy, to name a few (Speakman and Hambly, 2007).

4.1.1. Signaling pathways and epigenetic programming

Among biochemical pathways that are known to influence longevity pathways, GH/IGF1, Sirtuins and AMPK activators, have received great deal of attention. Manipulation of any or all of these pathways with proper pharmaceutical or nutritional supplements has been shown to increase life span through important genes and their pathways. For instance, two compounds, resveratrol and rapamycin are known to activate SIRT1 and mTOR pathways. Additionally, epigenetic changes, usually measured in terms of reaction norms at the level of individual phenotypes, could occur in response to a diverse array of factors: drugs, nutrients, climatic conditions and exercise as well as nutrients with antioxidant and anti-inflammatory effects (Bacalini et al., 2014; Myers and Williamson, 2014). Drugs such as metformin, a commonly prescribed medication against Type II diabetes, has shown some encouraging results toward increasing longevity via superior regulation of glucose levels (Barzilai et al., 2012).

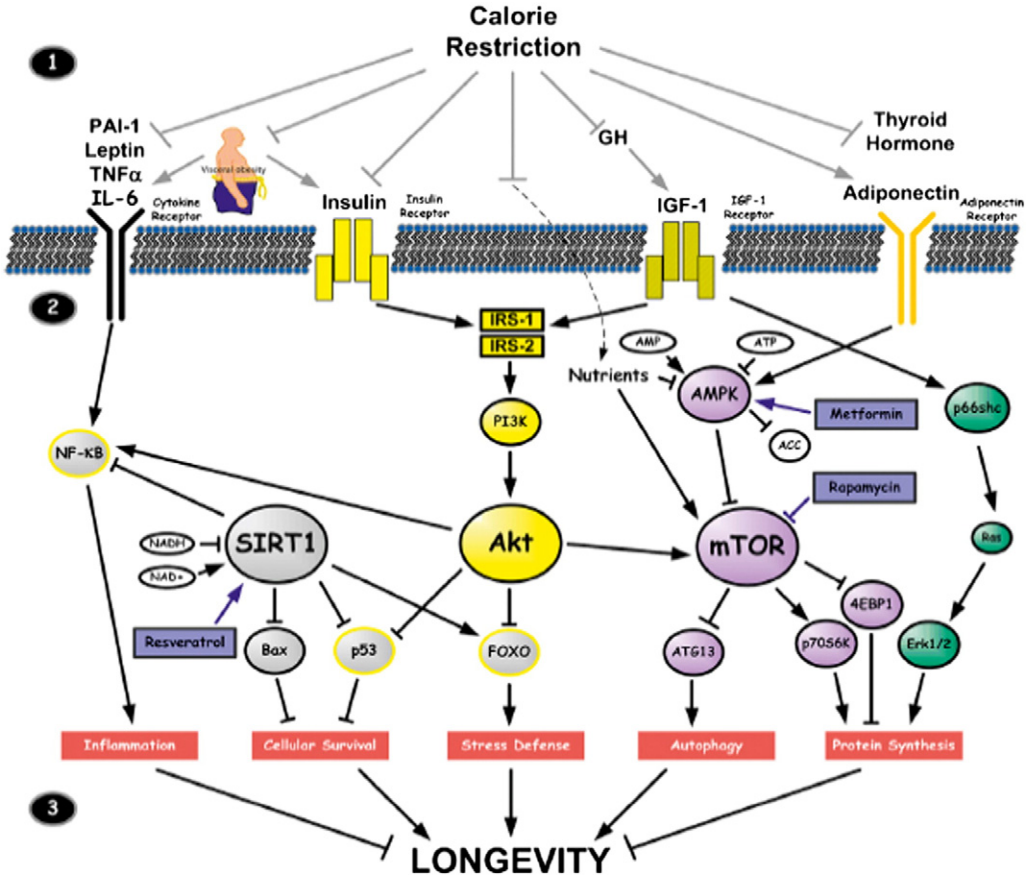

Fig. 3. Calorie restriction as an example of life-style modification and its plausible effects on the genetic–epigenetic–phenotypic spaces (Barzilai et al., 2012).

5. Centenarians

As discussed earlier, while the average life expectancy in the US is approaching 80 years, the mean life span of centenarians (and super-centenarians) is about 112 (Carey, 2003). As a group, they represent a distinct region of the demographic distribution among the contemporary human populations. In other words, assuming that the average human generation time is about 25 (Eyre-Walker and Keightley, 2009), centenarians are endowed with an extra human generation time. Besides, they are known to have a better health profile relative to the people with normal life span. These distinguishing features of centenarians have prompted an interest among demographers, health scientists and the general public alike, to explore the possibilities of extending the life span of cosmopolitan population to approach that of centenarians. Therefore, we consider their distinct features from an evolutionary, genetic, developmental and environmental perspective, as these factors have been suggested to influence quantitative traits universally. First, centenarians occur at a frequency of about 1.73 and 3.43 per 10000 individuals in the U.S. and Japan respectively (Meyer, 2010); hence they are rare. Second, among genetic factors, certain genotypes/alleles that are known to influence longevity are enriched among centenarians (e.g., Apo C3-CC; FOXO3a-T; CETP-VV; AdipoQ-del/del; TSHr-G and IGFr; (Barzilai et al., 2012); Fig. 4). Third, others have suggested that longevity may be a function of genomic integrity (e.g., Vijg and Suh, 2013). Although evidence on this important idea is relatively sparse on centenarians, Erceg et al. (2008) reported low levels of chromosomal aberrations (an index of superior genomic integrity), relative to cosmopolitan populations. They suggested that the relatively low level of chromosomal aberrations in the "oldest old" people may be both a consequence of their genomic stability and a contributing factor to their attainment of advanced age. This trend appears to hold even in nematodes, in which wild strains accumulated massive amounts of structural variants, but the long-lived daf-2 strain rarely did. Genomic instability is a well-known causal factor in progeric disorders (Misteli and Scaffidi, 2005). Fourth, similar trend seems to hold for epigenetic variation as well. For instance, Gentilini et al. (2013), compared methylation (epigenetic) patterns in centenarians and their progeny, and found that these patterns were "better preserved" in the progeny of centenarians than they were among controls. Collectively, these observations support the idea that genomic integrity may also influence both epigenetic and phenotypic integrity and contribute to either

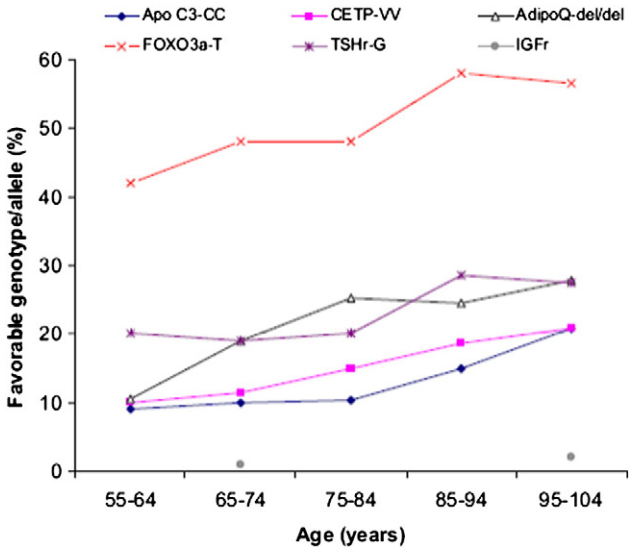

Fig. 4. Age related genotype frequencies of six genes in the Ashkenazi centenarian cohort (Barzilai et al., 2012).

acceleration or deceleration of longevity between individuals with ordinary or extraordinary life span, respectively. Fifth, at the phenotypic level, progeny of Okinawan and Ashkenazi centenarians have been shown to live longer and also have lower levels of cardiovascular diseases and lipid abnormalities, relative to their age-matched counterparts (Atzmon et al., 2005; Willcox et al., 2006). Sixth, from a biogeographical perspective, centenarians are found at a greater frequency at certain geographical regions of the world. These are called "Blue Zones" (Poulain et al., 2013), and are defined as "limited region(s) where the population shares a common lifestyle and environment and whose exceptional longevity has been accurately verified." In these zones, centenarians have been described to lead a distinct lifestyle, which includes greater intake of vegetables, stress free and active life-style, community bond and spirituality to list a few (Buettner, 2012). It is, therefore, assumed (and even recommended) that by following their suit, others in general populations could also aspire to maintain the prolonged health and longevity of these special people. This belief, however, may not be universally valid.

5.1. Origin and maintenance of centenarians in general populations

As discussed, centenarians are not only rare but also live for about an extra generation time, relative to the average life expectancy of global populations. In natural populations, rare morphs frequently arise and display greater fitness relative to the most common ones, as illustrated by negative frequency dependent selection (NFDS; Iserbyt et al., 2013). This form of selection has been suggested to be one of the evolutionary mechanisms by which rare traits are maintained (Moorad and Promislow, 2011). Rare individuals in large populations are known to possess superior physiological properties (Haldane, 1949). Occurrence of a rare phenomenon in nature as well as in the social sciences has been interpreted using the "Black Swan" metaphor (Taleb, 2007), suggesting that rarity in nature may be comparable to finding black swans in the 16th century London. Indeed, Vacante et al. (2012) have extended this concept to explain the occurrence of centenarians in general populations. In principle, the black swan concept is identical to frequency-dependent selection — a well-known evolutionary principle; which is qualitatively different from NFDS.

6. Discussion and conclusion

> "Nature is all that a man brings with himself into the world; nurture is every influence from without that affects him after his birth. … Neither of the terms implies any theory; natural gifts may or may not be hereditary; nurture does not especially consist of food, clothing, education, or tradition, but it includes all these and similar influences whether known or unknown." (Galton, 1890)

Like any quantitative trait, longevity is affected by genetic, developmental/epigenetic and environmental factors and shows tremendous amount of variation at all levels of biological hierarchies: among individuals, individuals within families and among families within populations. As a life history trait, it shows an ontogenetic relationship with other complex traits throughout the developmental course of an individual. Hence, longevity is both a composite and an emergent trait, influenced by the additive and multiplicative properties of many measured, latent and antecedent traits and at all the three spaces — genetic, epigenetic and phenotypic. Direct, indirect and mediation effects of many of these factors (as components of the G–E–P space) on longevity cannot be estimated independently of other traits, and often remain immeasurable due to their small and contextual effects, but can only be inferred. Therefore an integrated G–P map approach coupled with life-history provides a logical approach toward understanding the interplay among various components of genotype, epigenetic and phenotype space of longevity in relation to fixed and constructed environments.

At the genomic level, anywhere between 300–700 genes (or perhaps more) may be influencing longevity (Budovsky et al., 2013). Although this appears to be a large number, in a recent study on human height, which is arguably a less complex trait than longevity, Wood et al. (2014) reported that 697 variants among 423 genomic regions may be influencing the trait, and speculated that perhaps thousands may be involved. A similar argument could be advanced for longevity, because longevity as a life history and as an indeterminate trait, is influenced by traits that contribute to both viability and reproductive fitness from zygotic stage through adult stages, till death. Note that a number of genes that influence human height also influence longevity (e.g., IGF1 and mTOR) and other life-history traits, such as body weight and sexual maturity, due to pleiotropy. Life history traits often display genetic correlation due to the underlying pleiotropic effects of genes (Roff, 1997). Further, life history traits maintain allometric relationships, and consequently show trade-offs in their functional aspects (Carey, 2003; Stearns, 1992). Accordingly, genes that influence longevity could exert both differential and contextual influence on specific traits as well as correlated antecedent traits during the aging process, as shown by divergent patterns of methylation among age groups (Weidner and Wagner, 2014). These recent discoveries on the developmental regulation of aging, among contrasting age groups, using comparative gene expression, largely compliment previous reports on genotype–phenotype relationships (Hughes and Charlesworth, 1994; Mackay, 2009; Chevrud, 1988). On-going efforts to discover the functional role of large genomic regions (missed by using the more popular approaches — e.g. SNPs), using the discoveries from the ENCODE (Encyclopedia of DNA Elements) should advance our understanding of the cumulative contribution of genetic, epigenetic, phenotypic and environmental factors in aging and age-related disorders (Siggens and Ekwall, 2014; Ben-Avraham et al., 2012).

Longevity is inherently a highly plastic trait, and traits that influence its components respond to physical (static) environments and to wide ranging life-style changes: physical exercise, dietary habits, living conditions, and pharmaceutical as well as nutritional interventions. In fact, Krumholz et al. (2014) analyzed data on morbidity and mortality patterns of cardiovascular diseases among 34 million Americans from 1999–2000, and found that hospitalizations due to heart attack and stroke have reduced to 38 and 34%, respectively. They attributed this dramatic success to lifestyle changes, better treatment and preventive measures (sensu, Egger and Dixon, 2014), rather than any major innovations. Needless to state, both recommended and self-motivated life style changes in order to reduce cardiovascular disease risks, must have also contributed to the overall health and longevity of at least a fraction of the U.S. population. Clearly, such life-style changes represent novel dimensions of "constructed" environments (niche construction; Borenstein et al., 2006). Niche construction provides unique perspective about "thinking of phenotypes as being reconstructed in each generation by different developmental resources (genetic and non-genetic), rather than as an expression of genetically enclosed information only" (Odling-Smee et al., 2013). Interestingly, niche construction appears to follow the "rich-get-richer rule" (Borenstein et al., 2006). A number of "macro-social" (economic, social and ecological) factors that contribute to this rule are still influencing and will continue to influence public health (Galea and Putnam, 2007), ultimately contributing toward increased life span (sensu, Finch 2007). Unsurprisingly, there is also a greater concentration of nonagenarians and centenarians, in areas/populations that already foster a large number of nonagenarians, which are also concentrated clusters of macro-social factors. To generalize, and in accordance with the theory of niche construction, we suggest that novel and sustained NC activities might have contributed to differential, nonetheless increasing trend in life expectancy among human population worldwide, in the last five centuries (Finch, 2007; Vaupel, 2010) and these would continue to influence in the future. This scenario also agrees well with the evolution of reaction norms in relation to changing

environments (Stearns, 2014). Clearly, niche construction would also influence the evolution of reaction norms, which in turn would promote evolutionary changes (Stearns, 2014).

The biological basis of exceptional health and longevity among centenarians has remained unclear. The general features of exceptional longevity, however, appears to run in families, and as a group they have a natural tendency to maintain good health much of their lives. Although centenarians are found to occur at higher frequencies in certain geographical locations, or "blue zones," their life-style may not be significantly different from individual members of cosmopolitan populations who chose to lead a healthy life-style. It is likely that centenarians differ from each other just as individuals with normal life span do. Yet, individuals with exceptional longevity may interact with environmental and lifestyle factors differently than others (Rajpathak et al., 2011). This unique feature may be interpreted as a form of genotype × environment interaction (Falconer and Mackay, 1996). As a parsimonious explanation, from a genomic perspective, exceptional longevity of centenarians may be attributed to their superior genomic integrity, specific polymorphisms among genes such as ApoC3-CC, FOXO3aT, and CETPVV, and associated molecular genetic and physiological homeostatic mechanisms. It is likely that centenarians arise and are maintained by negative frequency-dependent selection, as this mode of selection has been shown to have slightly superior physiological mechanisms relative to more common genotypes in general populations. There may be other mechanisms, however, and needs further investigation. These rare individuals may also contribute to cultural transmission as an aspect of niche construction, which may further contribute to fitness of individuals, families and populations across generations (Cavalli-Sforza and Feldman, 1981; Laland, 2014; Govindaraju et al., 2014).

Encouraged by the fact that life span has increased over the last two centuries (and on the basis of the discovery of long-lived mutants in model organisms, due to genetic modification or dietary changes or both), there is a popular belief that longevity could be increased linearly (and almost limitlessly) with life-style modification. This notion may be traced to the success met with improving quantitative traits in model organisms and in various plant and animal species through diverse breeding techniques, in which a combination of genetic and environmental factors have been employed to make spectacular progress in improving specific traits. Unfortunately, many theoretical and empirical studies dealing with long-term selection on various organisms have consistently shown that sustained selection would lead to a plateau (Goodnight, 2014), and some have even become unresponsive despite genetic and environmental manipulations (e.g., Grassini et al. (2013)). These results compliment the fact that enzyme and coenzyme complexes that moderate gene action among gene networks in the epigenetic space invariably show rate-limiting properties (Wright, 1934; Kacser and Burns, 1981; Fievet et al., 2006). Longevity as a composite trait is correlated with other complex traits and their components; hence composite traits work as a system of systems. Accordingly, genetic response to selection on such correlated complexes of traits is jointly determined by genetic variances among individual traits and their covariances (Walling et al., 2014). Thus, it is unlikely, that longevity could be extended to a great extent as popularly claimed, without effecting substantial changes in a system of other life-history traits.

In conclusion, although both normal and exceptional longevity are influenced by similar genetic, epigenetic and environmental factors, life-style factors could exert advantageous and deleterious, as well as differential effects on longevity at all the three spaces — genetic, epigenetic and phenotypic. These changes could be measured using systems and reaction norm approaches. It appears that lifestyle changes at the individual, family and population levels may have contributed disproportionately to world-wide increase in human longevity in the last few centuries. In other words, as Ridley (2003) has pointed out, nurture appears to have shaped the nature of human longevity in the modern human societies. This phenomenon could be explained fairly satisfactorily by extending the theory of niche construction and the concept of developmental plasticity. Accordingly, appropriate lifestyle changes hold promise toward increasing longevity (at least to a limited extent) at all levels of human diversity. Exceptional longevity, as a threshold trait, may be governed by negative frequency dependent selection. This mode of selection adequately explains the maintenance of superior genomic integrity and homeostatic mechanisms, across genomic–epigenetic–phenotypic spaces, for a much longer period in centenarians than in individuals with normal life span. In accordance with the original Wright–Waddington scheme (Wright, 1921, 1934; Waddington, 1942, 1957), we suggest that extending causal analytical approaches (e.g., Pearl, 2009) to include sequential developmental architecture among traits, would prove useful to understand: a) the latent, emergent, contextual and hierarchical aspects of genotype-epigenetic-phenotype (GEP landscape; Lewontin, 1974) spaces, and b) the coordinated and functional relationships among the determinants of health and longevity over the entire life-course of individuals. For instance, Chen et al. (2012) employed a comprehensive systems approach to synthesize genetic, proteomic, phenotypic and demographic data to predict and treat Type II diabetes during the course of its development in an individual, essentially reversing or managing the disease progression. Such integrated approaches are gaining popularity in the development of predictive and preventive medicines which would significantly impact health and longevity of individuals and populations (e.g., Topol, 2014). Keeping these advances in perspective, Johnston (2014) recently commented that humans are indeed emerging as a model organism. In fact, recent developments in human genetics indicate that the use of conventional model organisms to study healthy life span in humans and to improve human condition, could be displaced with humans themselves, affirming Alexander Pope's prophetic words, "The proper study of Mankind is Man."

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